

PATENT SPECIFICATION
NO DRAWINGS

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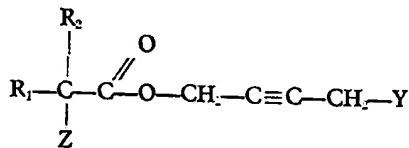
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International Classification:—C 07 c.

COMPLETE SPECIFICATION

Aminoacetylenes and Process for Preparing the Same

- We, MEAD JOHNSON & COMPANY, a corporation organized under the laws of the State of Indiana, United States of America, of Evansville, State of Indiana, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:
- 5 The present invention relates to certain aminoacetylenes, processes for preparing them, and the pharmaceutically-acceptable acid-addition salts thereof.
- 10 Specifically, the present invention provides a compound having the general formula
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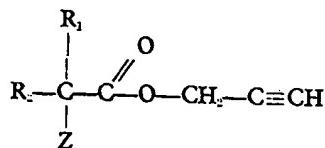


wherein R_1 is a phenyl, benzyl, cyclohexyl or alpha-thienyl group; R_2 is a phenyl or benzyl group; Z is a hydrogen atom or a hydroxyl, methoxy, ethoxy or methylthio group; and Y is a di- C_1 to C_6 -alkylamino, piperidino, pyrrolidino or morpholino group; and the pharmacologically-acceptable acid-addition salts of these compounds.

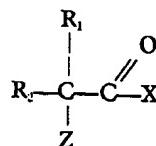
20 Preferably, Y is a dialkylamino group containing 2 to 6 carbon atoms and preferably R_1 is phenyl or benzyl in such cases.

The present invention also provides a process for preparing a compound as defined [Price]

above which comprises reacting a derivative of 1-propyne-3-ol having the general formula



with formaldehyde (e.g. in the form of paraformaldehyde) and a compound of the general formula $H-Y$; or reacting a compound of the general formula



with a compound of the general formula



wherein in the above formulae R_1 , R_2 , Y and Z are as defined above and Z may also be a halogen atom, X is a halogen atom or a C_1 to C_6 alkoxy radical and R_3 is a hydrogen atom or a formyl, acetyl or propionyl group, and, where Z is a halogen atom, hydrolytically cleaving Z to form the corresponding product wherein Z is a hydroxyl group.

In a preferred embodiment of the second

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part of the above-defined process wherein X is chlorine, R_c is hydrogen, Y is a piperidino, pyrrolidino or morpholino group, the acyl chloride is reacted with the 4-amino-5 butynol in the presence of an alkaline reaction medium.

The pharmacologically acceptable acid-addition salts may be prepared by reacting the compound with the acid corresponding to the acid radical in the required acid-addition salt.

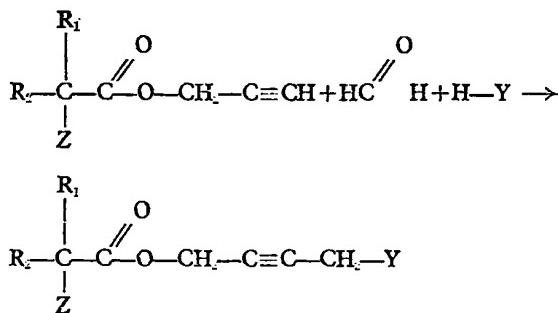
The compounds of the present invention have utility as antispasmodics and local anaesthetics. The dosage for mammals is from 0.1 to 5.0 milligrams per kilogram of body weight in the case of administration for

the relief of muscle spasms. The compounds may be administered orally in the form of elixirs, tablets, powders, suspensions or the like, or may be administered intravenously. When used as local anaesthetics the compounds are preferably administered topically or by infiltration of the tissue at concentrations of, 0.25% to 2.0%. 20

The preparation of the compounds of this invention is described herein below. 25

METHOD A

This method comprises a modified Mannich reaction of an acetylene with an aldehyde and an amine. The reaction proceeds as follows: 30



wherein R₁, R₂ and Z are as previously defined and Y as a di-C₁ to C₆-alkylamino group, or a piperidino, pyrrolidino or morpholino group. 35

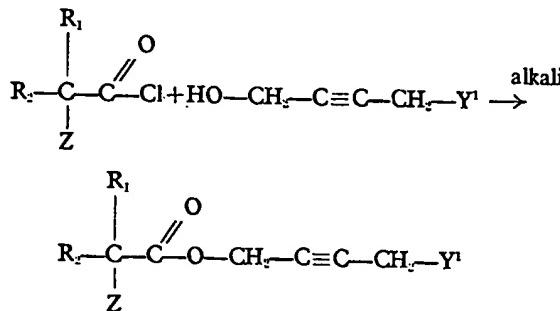
The group Z may also be a halogen atom and, where it is, is hydrolytically cleaved to the corresponding product wherein Z is a hydroxyl group. The following examples indicate the preparation of certain of these compounds by Method A. 40

EXAMPLE I
4 - DIMETHYLAMINO - 2 - BUTYNYL DI-PHENYLACETATE HYDROCHLORIDE. — Para-formaldehyde, 1.56 g. (0.052 mole), and 2.0 g. (0.044 mole) of dimethylamine were dissolved in 10 ml. of dry dioxane and allowed to stand at room temperature for ten minutes. A solution of propargyl di-phenylacetate, 10 g. (0.04 mole) dissolved in 25 ml. of dry dioxane, was then added to the reaction mixture and the mixture was heated on a steam bath for seventeen hours under an atmosphere of nitrogen. The reaction mixture was allowed to cool slightly, and the unreacted dimethylamine was removed by evaporation under reduced pressure. Hydrochloric acid (2 N) was then added to the mixture, and the resultant acidic

solution was washed with ether. The acidic solution was cooled with crushed ice and basified with 10% sodium hydroxide solution. The insoluble oil which precipitated was taken up in ether and the ether solution was dried over magnesium sulphate. The drying agent was filtered off and dry hydrochloric acid was passed into the solution to precipitate the hydrochloride salt: m.p. 180—181.5° C. (dec.) from n-propanol. 55

EXAMPLE II
4 - PYRROLIDINO - 2 - BUTYNYL DI-PHENYLACETATE HYDROCHLORIDE. — This compound was prepared by the procedure of Example I, using however pyrrolidine in place of the dimethylamine (in the same molar proportion). The reactants were heated on the steam bath for 40 hours. The hydrochloride salt of the product crystallized from ethylacetate-propanol melted at 140—142° C. 75

METHOD B:
This method comprises the esterification by the reaction of acyl halides and 4-substituted-amino-2-butynols in alkaline reaction media typified by the following equation in which the acyl halide is an acyl chloride: 80



wherein R_1 , R_2 and Z are as previously defined, and Y' is a pyrrolidino, piperidino or morpholino group. In a particular embodiment of Method B, the acyl halide may have an alpha-halo substituent. In this embodiment the esterification is conducted as above and after the esterification the alpha-halogen atom is hydrolytically cleaved from the ester product to produce a compound in which the substituent Z is a hydroxyl group. The following Examples illustrate preparation of these products by Method B and the particular embodiment thereof.

EXAMPLE III

4 - PIPERIDINO - 2 - BUTYNYL DIPHENYL ACETATE HYDROCHLORIDE. — Fifteen grams (0.065 mole) of diphenylacetylchloride was slowly added to 10.0 g. (0.065 mole) of 4 - piperidino - 2 - butynol [prepared by the reaction of 1-chloro-4-hydroxy-2-butyne and piperidine (b.p. 116° C., 1.4 mm. Hg. (abs.); $n_{D}^{20} 1.5094$)], dissolved in 30 ml. of dry pyridine. An exothermic reaction followed and subsided after five to ten minutes. The reaction mixture was then heated on a steam bath for one hour, cooled and poured onto crushed ice and water. The resultant aqueous solution was extracted with two 50 ml. portions of ether and the extracts were combined and washed with several 10-ml. portions of 2 N hydrochloric acid until most of the residual pyridine was removed. The ether solution was washed with water and dried over magnesium sulphate. The drying agent was filtered off and dry hydrochloric acid was passed into the ether solution to form the hydrochloride salt of the expected product. The hydrochloride salt was washed with dry ether and recrystallized from ethyl acetate; m.p. 155—156.50° C.

EXAMPLE IV

4 - PYRROLIDINO - 2 - BUTYNYL BENZILATE HYDROCHLORIDE. — α - Chlorodiphenylacetylchloride, 17.2 g. (0.065 mole) was dissolved in about 40 ml. of dry pyridine and 7.0 g. (0.065 mole) of 4-pyrrolidino-2-butynol [prepared by the reaction of 1-chloro-4-hydroxy-2-butyne and

pyrrolidine (b.p. 98—104° C., 1.0 mm. Hg. (abs.); $n_{D}^{20} 1.5055$)] was slowly added to the solution with stirring. When the ensuing vigorous reaction subsided, the mixture was heated on a steam bath for one-half hour.

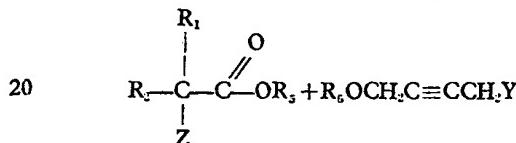
The reaction mixture was then poured onto crushed ice and water and the resulting aqueous mixture was extracted with ether. The combined ether extracts were washed with water, extracted with 2 N hydrochloric acid, and the acidic extract was heated on a steam bath for five minutes. The mixture was cooled and basified with 10% sodium hydroxide. The viscous oil which separated from the aqueous solution was taken up in ether and the ether was dried over magnesium sulphate. The drying agent was filtered off and the ether was evaporated, leaving a pale yellow solid. Trituration with ether removed the yellow impurity; m.p. 108—111.5° C. from aqueous ethanol.

The free base was partially dissolved in anhydrous ether and dry hydrochloric acid was passed into the solution. The resulting hydrochloride salt was filtered onto a Buchner funnel, washed with ether, dried, and recrystallized from ethyl acetate-ethanol; m.p. 132.5—134.5° C.

EXAMPLE V

4 - PIPERIDINO - 2 - BUTYNYL DIPHENYL ISOBUTYRATE HYDROCHLORIDE.—Diphenylisobutryl chloride, 18.1 g. (0.07 mole) and 21.0 g. (0.21 mole) of triethylamine were cautiously mixed with 85 ml. of anhydrous benzene. To this stirring mixture, 10.1 g. (0.07 mole) of 4-piperidino-2-butynol, dissolved in 20 ml. of dry benzene was added dropwise. After the addition of the amino alcohol was completed, the reaction mixture was heated on the steam bath for three hours, cooled and poured onto crushed ice and water. The organic layer was separated, washed with water, and extracted with several 5-ml. portions of 2 N hydrochloric acid until the extracts began to contain product (the extracts were made basic to check if product was being extracted). After all excess triethylamine was removed by the method just described, the benzene solution was extracted

with 2 N hydrochloric acid. The acidic extracts were combined, cooled in an ice bath, and made strongly basic with 10% sodium hydroxide. An oil separated which was taken up in ether. The ether solution was washed with water and dried over magnesium sulphate. The drying agent was filtered off and dry hydrochloric acid was passed into the ether solution to precipitate the hydrochloride salt of the desired product.



wherein R_1 , R_2 , Z and Y are as described above, R_3 is a C_1 to C_6 alkyl group, for example a methyl, ethyl, n-propyl, or isopropyl group, and R_4 is hydrogen or a formyl, acetyl, or propionyl group. The reaction is carried out preferably by heating the two reactants in the presence of a transesterification catalyst, for example sodium or potassium metal, or a lower alkoxide thereof, for example sodium methoxide, sodium ethoxide, or potassium t-butoxide. The group Z may also be a halogen atom and, where it is, Z is hydrolytically cleaved to the corresponding product wherein Z is a hydroxyl group.

35 The following examples illustrate Method C.

EXAMPLE VI

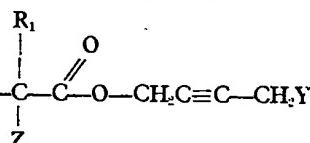
4 - PYRROLIDINO - 2 - BUTYNYL - α - METHYLTHIODIPHENYLACETATE HYDRO-40 CHLORIDE.—Methyl - α - methylthiodiphenylacetate, 9.5 g. (0.035 mole) and 4.9 g. (0.035 mole) of 4-pyrrolidino-2-butynol were dissolved in 150 ml. of n-heptane, and about 50 mg. of sodium methoxide catalyst was added. The mixture was stirred and refluxed, and the heptane-methanol azeotrope was collected in a Dean Stark trap. After 0.4 ml. of azeotrope was collected in the trap, the reaction appeared to stop. The reaction mixture was cooled slightly, additional catalyst was added, and refluxing was resumed. The total amount of azeotrope collected was 0.85 ml. (theory, 1.1 ml.).

55 The reaction mixture was cooled, poured onto ice and water and the organic layer was separated and washed with water. The heptane solution was then extracted with 2 N hydrochloric acid and the acidic extract was washed with ether and then made alkaline with 10% sodium hydroxide. The freed base was then taken up in ether, and the ether solution was washed with water and dried over magnesium sulfate. The drying agent was filtered off and dry hydrochloric acid was passed into the ether solution to precipitate the hydrochloride salt: yield, 5.4

The hydrochloride was recrystallized from benzene, m.p. 156.5—158.5° C.

METHOD C:

This method of preparing the compounds of the present invention comprises transesterification of a lower alkyl ester of a substituted acetic acid with a substituted aminobutyrol or lower aliphatic ester thereof according to the equation:



g., m.p. 154—156° C., from isopropyl alcohol.

EXAMPLE VII

4-DIMETHYLAMINO-2-BUTYNYL BENZILATE HYDROCHLORIDE.—This compound was prepared by the method of Example VI from methyl benzilate and 4-dimethylamino-2-butynol [the latter prepared by reaction of 1-chloro-4-hydroxy-2-butyne and dimethylamine: b.p. 80—84° C. (0.55 mm.) n_D^{20} 1.4764] using sodium metal catalyst. The free base product recrystallized from heptane melted at 102.5—105° C. The hydrochloride salt recrystallized from ethylacetate-ethanol melted at 130—133° C.

EXAMPLE VIII

4-DIETHYLAMINO-2-BUTYNYL BENZILATE HYDROCHLORIDE.—This compound was prepared by the method of Example VI, from 4-diethylamino-2-butynol and methyl benzilate, using sodium metal as catalyst for the transesterification reaction. The intermediate was prepared as follows:

To a stirring solution of 41.7 g. (0.57 mole) of diethylamine and 60 ml. of anhydrous benzene was added (within a few minutes) 24.5 g. (0.23 mole) of 1-chloro-4-hydroxy-2-butyne. The ensuing reaction was exothermic causing the reaction mixture to reflux. After the initial reaction subsided, the reaction mixture was refluxed for fifteen minutes and then allowed to cool to room temperature with continual stirring. The solid diethylamine hydrochloride was filtered off and the benzene was removed under reduced pressure. The residual oil was distilled in vacuo: b.p. 85—90° C. (0.45—0.5 mm.); n_D^{20} 1.4793; yield, 25.2 g. (76.5%).

The hydrochloride salt of 4-diethylamino-2-butynyl benzilate, recrystallized from ethylacetate-ethanol, melted at 128.5—130.5° C.

EXAMPLE IX

4 - PIPERIDINO - 2 - BUTYNYL BENZILATE HYDROCHLORIDE.—This compound was pre-

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pared by the method of Example VI using sodium metal as a transesterification catalyst, from the methyl benzilate and 4-piperidino-2-butynol. The free base from heptane 5 melted at 111.5—115° C. The hydrochloride salt recrystallized from ethylacetate-ethanol, melted at 141.5—144° C.

EXAMPLE X

4 - MORPHOLINO - 2 - BUTYNYL BENZIL-
ATE HYDROCHLORIDE.—This compound was
prepared by the method of Example VI using
sodium metal catalyst from methyl benzilate
and 4-morpholino-2-butynol. [The 4-
morpholino-2-butynol was prepared by re-
action of morpholine and 1-chloro-4-hydroxy-
2-butyne, b.p. 119—124° C. (0.9 mm.);
 n_{D}^{20} 1.5091.] The free base from ethanol
melted at 117.5—120° C. The hydrochloride
salt recrystallized from ethylacetate-ethanol
20 melted at 158—160° C.

EXAMPLE XI

4 - DIETHYLAmino - 2 - BUTYNYL - α -
METHYLTHIODIPHENYLACETATE HYDRO-
CHLORIDE.—This compound was prepared by
the method of Example VI from methyl- α -
methylthiodiphenylacetate [Becker et al. *Ber.*
47, 3149 (1914)], and 4-diethylamino-2-
butynol. The hydrochloride recrystallized
from ethyl acetate-ethanol, melted at 146—
30 148° C.

EXAMPLE XII

4 - PIPERIDINO - 2 - BUTYNL - α -
METHYLTHIODIPHENYLACETATE HYDRO-
CHLORIDE.—This compound was prepared by
the method of Example VI from methyl- α -
methylthiodiphenylacetate and 4-piperidino-2-
butynol. The hydrochloride salt recrystallized
from ethyl acetate: petroleum ether (Skelly-
solve B, b.p. 63—69° C.), melted at 171.5—
40 173° C. Other salts were nitrate, m.p.
131.5—133.5° C., monohydrogen tartrate,
m.p. 120—122.5° C., tartrate, m.p. 99—
102° C.

EXAMPLE XIII

4 - MORPHOLINO - 2 - BUTYNYL - α -
METHYLTHIODIPHENYLACETATE HYDRO-
CHLORIDE.—This compound was prepared by
the procedure of Example VI from methyl- α -
methylthiodiphenylacetate and 4-morpholino-
50 2-butynol. The hydrochloride salt recrystallized
from ethyl acetate-ethanol melted at
171—173.5° C.

EXAMPLE XIV

4-DIETHYLAmino-2-BUTYNYL PHENYL-
 α -THIENYLGLYCOLATE HYDROCHLORIDE.—
This compound was prepared by the method
of Example VI from the methyl ester of
phenyl - α - thietylglycolic acid [Fischer
esterification of the acid (Blicke & Tsao,
J. Amer. Chem. Soc., 66 1645 (1944)) gave
60 the ester; b.p. 130—133° C (0.65 mm.)
 n_{D}^{20} 1.5709], and 4-diethylamino-2-butynol.

The hydrochloride salt recrystallized from
ether-benzene, pressure bottle, melted at
81.5—83.5° C.

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EXAMPLE XV

4-DIETHYLAmino-2-BUTYNYL PHENYL-
CYCLOHEXYLGLYCOLATE HYDROCHLORIDE.—
This compound was prepared by the method
of Example VI from the methyl ester of
phenylcyclohexylglycolic acid [the ethyl ester
of phenylcyclohexylglycolic acid—Smith et al.
J. Amer. Chem. Soc. 75, 2654 (1953)—was
converted to the methyl ester by hydrolysis
followed by esterification; b.p. 114—119° C.
(0.45 mm.); n_{D}^{20} 1.5247] and 4-diethylamino-
2-butynol. The hydrochloride salt recrys-
tallized from ethylacetate melted at 129—
130° C.

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EXAMPLE XVI

4 - PIPERIDINO - 2 - BUTYNYL - α - METH-
OXYDIPHENYLACETATE HYDROCHLORIDE.—
This compound was prepared by the method
of Example VI using metallic sodium as a
catalyst from methyldiphenylmethoxyacetate
and 4-piperidino-2-butynol. The hydro-
chloride salt recrystallized from ethyl acetate-
ethanol melted at 170.5—172° C.

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EXAMPLE XVII

4 - PIPERIDINO - 2 - BUTYNYL - α - ETH-
OXYDIPHENYLACETATE HYDROCHLORIDE.—
This compound was prepared by the pro-
cedure of Example VI from methyldiphenyl-
ethoxyacetate [prepared by Williamson ether
synthesis from equimolar amounts of α -
bromo-methyl-benzoate and sodium ethoxide;
b.p. 130—137° C., (0.55 mm.), n_{D}^{20} 1.5454],
and 4-piperidino-2-butynol. The hydro-
chloride salt recrystallized from ethyl acetate-
ethanol melted at 173.5—175° C.

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EXAMPLE XVIII

4-DIETHYLAmino-2-BUTYNYL PHENYL-
CYCLOHEXYLGLYCOLATE HYDROCHLORIDE.—
A mixture of 394.2 g. of methyl phenyl-
cyclohexylglycolate, 293.1 g. of 4-diethyl-
amino-2-butynyl acetate was dissolved with
warming in 2.6 l. of n-heptane. The solu-
tion was heated with stirring to a tempera-
ture of 60—70° C. and 8.0 g. of sodium
methoxide were added. The temperature of
the mixture was then raised until the sol-
vent began to distil. Distillation was con-
tinued at a gradual rate and aliquots of
the distillate were successively collected
and analyzed for the presence of methyl
acetate by measurement of the refractive
index. The reaction was completed when
methyl acetate no longer distilled, and the
refractive index observed was that of pure
heptane (n_{D}^{20} 1.3855). About three and
one-half hours were required for the reaction
to be completed. The reaction mixture was
then allowed to cool to room temperature,
washed with water, and extracted with four

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165 ml. portions of 2 N hydrochloric acid. The aqueous extracts were combined and stirred at room temperature to permit crystallization of the hydrochloride salt of the desired product. Crystallization was completed by cooling the slurry in an ice bath, and the product was collected by filtration, pressed dry, and recrystallized from 750 ml. of water. Yield of pure crystalline material, 10 323 g.

METHOD D

In this method, an alpha-methoxydiphenylacetate or an alpha-ethoxydiphenylacetate of a 4-substituted amino-2-butynol of the 15 formula



wherein Y is a di-C₁ to C₆-alkylamino, piperidino, pyrrolidino or morpholino radical, is prepared by heating and reacting a 4-substituted amino-2-butynol as above described 20 with an alpha-halodiphenylacetyl halide and thereafter treating the reaction product with methanol or ethanol in an alkaline reaction medium and recovering the alpha-methoxy-diphenyl acetate or alpha-ethoxydiphenylacetate product.

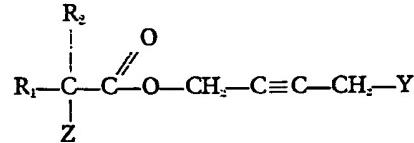
The following Example illustrates Method D.

EXAMPLE XIX

30 4 - DIMETHYLAMINO - 2 - BUTYNYL - ALPHA-ETHOXY DIPHENYLACETATE HYDRO-CHLORIDE.—Equivalent amounts of alpha-chlorodiphenylacetyl chloride, 11.4 g. (0.043 mole), and 4-dimethylamino-2-butynol, 4.9 g., 35 were mixed in a 100 ml. flask and heated with an oil bath at 100 to 105° C. for twenty-five minutes. Heating was continued at 70° C. for thirty minutes. The resultant brown viscous oil was washed thoroughly with 40 anhydrous ether and then dissolved in 100 ml. of anhydrous ethanol. The ethanolic solution was refluxed for twenty-five hours with 5 g. sodium carbonate. The reaction mixture was cooled, filtered and made basic with 10% sodium hydroxide. Most of the ethanol 45 was then removed under reduced pressure with the aid of a steam bath and the resultant aqueous mixture was extracted with ether. The ether layers were combined, washed with water and dried over magnesium sulphate. 50 Anhydrous hydrogen chloride was then passed into the ether solution to prepare the hydrochloride salt; yield, 4.0 g. (24%); mp. 166.5—168.5° C., from ethyl acetate-ethanol. While certain specific acid addition salts 55 were shown in the foregoing examples, it should be understood that other nontoxic pharmacologically acceptable acid addition salts, such as hydrobromides, hydroiodides, sulphates, phosphates, acetates, citrates, succinates, and benzoates can be readily prepared by techniques well known in the art.

WHAT WE CLAIM IS:—

1. A compound having the general formula



wherein R₁ is a phenyl, benzyl, cyclohexyl or alpha-thienyl group; R₂ is a phenyl or benzyl group; Z is a hydrogen atom or a hydroxyl, methoxy, ethoxy or methylthio groups; and Y is a di-C₁ to C₆-alkylamino, piperidino, pyrrolidino or morpholino group; and the pharmacologically acceptable acid addition salts of these compounds. 65

2. A compound of the general formula given in claim 1 wherein Y is a dialkylamino group containing from 2 to 6 carbon atoms. 70

3. A compound according to claim 2, wherein R₁ is phenyl or benzyl.

4. 4-Di-C₁ to C₆-alkylamino-2-butynylbenzilates.

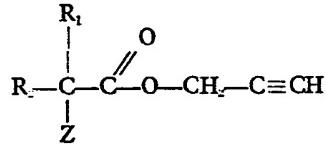
5. 4-Di-C₁ to C₃-alkylamino-2-butynylbenzilates. 80

6. 4-Diethylamino-2-butynyl-phenylcyclohexylglycolate.

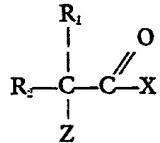
7. 4-Diethylamino-2-butynyl-benzilate.

8. 4-Piperidino-2-butynyl-alpha-methylthiophenylacetate. 85

9. A process for preparing a compound according to claim 1 which comprises reacting a derivative of 1-propyne-3-ol having the general formula



with formaldehyde (e.g. in the form of para-formaldehyde) and a compound of the general formula H—Y; or reacting a compound of the general formula



with a compound of the general formula



wherein in the above formulae R₁, R₂, Y and Z are as defined in claim 1 and Z may also be a halogen atom, X is a halogen atom or a C₁ to C₆ alkoxy radical and R₆ is a hydrogen atom or a formyl, acetyl or pro-

pionyl group, and, where Z is a halogen atom, hydrolytically cleaving Z to form the corresponding product wherein Z is a hydroxyl group.

5 10. A process according to the second part of claim 9 wherein X is chlorine, R₁ is hydrogen, Y is a piperidino, pyrrolidino or morpholino group, and the acyl chloride is reacted with the 4-aminobutynol in the presence of an alkaline reaction medium.

10 11. A process according to the second part of claim 9 wherein X is a C₁ to C₆ alkoxy radical and R₁, R₂, R₃, Y and Z are as defined therein, the compounds being reacted in the presence of a transesterification catalyst.

15 12. A process for preparing an alpha-methoxydiphenyl acetate or alpha-ethoxydiphenyl acetate of a 4-substituted amino-2-butynol of the general formula.



wherein Y is a di-C₁ to C₆- alkylamino,

piperidino, pyrrolidino or morpholino radical, which comprises heating and reacting a 4-substituted amino-2-butynol of the said general formula with an alpha-halodiphenyl acetyl halide, treating the reaction product with methanol or ethanol in an alkaline reaction medium and recovering the product of the process.

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13. A process for preparing a pharmaceutically acceptable acid-addition salt of a compound prepared in accordance with any one of claims 9 to 12 which comprises reacting the said compound with the acid corresponding to the acid radical in the required acid-addition salt.

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14. A process for preparing a compound according to any of claims 1 to 8, substantially as herein described with particular reference to the Examples.

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STEVENS, LANGNER, PARRY AND
ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1963.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

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